OPHTHALMIC COMPOSITIONS CONTAINING COPOLYMERS OF SULFONATED STYRENE AND MALEIC ANHYDRIDE

This application claims priority to U.S. Provisional Application, Ser. No. 60/301,569, filed June 27, 2001.

BACKGROUND OF THE INVENTION

The present invention relates to pharmaceutical compositions comprising a sulfonated styrene/maleic anhydride copolymer. In particular, the present invention relates to comfortable, preserved, topically administrable, aqueous solutions containing a cationic drug and a sulfonated styrene/maleic anhydride copolymer in an amount sufficient to enhance the comfort and/or solubility of the drug.

Pharmaceutical solution compositions are generally preferred over suspension compositions because they are easier to manufacture and process, and because they generally cause less irritation and foreign body sensation when topically applied to the eye. Surfactants and polymers can be added to compositions containing an insoluble drug in an attempt to increase the drug's solubility. For example, as disclosed in U.S. Pat. No. 5,679,336, polystyrene sulfonic acid polymers can be added to topically administrable compositions containing the ophthalmic antibacterial drug ciprofloxacin in order to permit such compositions to be formulated at approximately neutral pH. Previously, aqueous formulations of ciprofloxacin were formulated at acidic pH (approximately pH 4.5) because ciprofloxacin is not soluble at desired levels in simple aqueous compositions at approximately physiological pH (pH 6.0–7.5). Topically administrable ophthalmic compositions that must be formulated at a pH below 6.0 are generally less comfortable than similar compositions that are formulated at approximately physiological pH.

In some cases, ophthalmic drugs that are sufficiently soluble to be formulated as solutions at physiological pH are nevertheless uncomfortable. U.S. Pat. No. 4,911,920 discloses betaxolol compositions containing a water-insoluble ion exchange resin that enhances comfort and provides some extended drug release relative to similar compositions that do not contain such resins. Betoptic® S is a betaxolol product commercially available from Alcon Laboratories, Inc. that incorporates the ion exchange resin known as Amberlite IRP-69, a sodium poly(styrene-divinyl benzene) sulfonate product commercially available from Rohm & Haas.

Although both approaches mentioned above are successful, neither is ideal. Topically administrable ophthalmic compositions formulated as multi-dose products typically contain an ophthalmically acceptable cationic preservative. Solution compositions that contain water-soluble polystyrene sulfonic acid can be difficult to preserve because the negatively charged polystyrene sulfonic acid polymer interacts with the cationic preservative, reducing the preservative's ability to function as a preservative. Suspension compositions containing a water-insoluble resin to enhance comfort are more difficult to manufacture and process than solution compositions.

SUMMARY OF THE INVENTION

The present invention provides aqueous pharmaceutical solution compositions. The compositions are particularly well suited for topical ophthalmic use, but may also be used as topically administrable otic or nasal compositions. The compositions are preserved with a cationic preservative and comprise a cationic drug and a sulfonated styrene/maleic anhydride copolymer.

Among other factors, the present invention is based on the finding that solution compositions comprising a sulfonated styrene/maleic anhydride copolymer are easier to preserve than similar compositions comprising polystyrene sulfonic acid.

DETAILED DESCRIPTION OF THE INVENTION

Unless indicated otherwise, all component amounts are presented on a % (w/w) basis.

The pharmaceutical compositions of the present invention comprise a cationic drug compound. The compositions of the present invention may comprise any pharmaceutically acceptable drug compound, but preferred are compounds that comprise both a ring structure and an amine functional group. The ring structure in the preferred compounds may be any ring, but is preferably a cydoalkyl or an aromatic ring, with compounds containing benzyl or other aromatic rings being the most preferred. Such preferred compounds include, but are not limited to, betaxolol, levobetaxolol, ciprofloxacin, olopatadine and their pharmaceutically acceptable salts. The compositions of the invention are best suited for drug compounds for which enhanced solubility or comfort is desirable.

Sulfonated styrene/maleic anhydride copolymers (and their salts) are known. See for example, U.S. Pat. No. 4,450,261, the entire contents of which are hereby incorporated by reference in the present specification. Multiple grades of sulfonated styrene/maleic anhydride copolymers are commercially available, including those available as Versa TL-3 (weight average molecular weight=20,000), Rs aqueous solution form Versa TL-4 (25% w/w Versa TL-3), and Versa TL-7 (weight average molecular weight=15,000) from Alco Chemical, a division of National Starch and Chemical Co. (Chattanooga, Tennessee). Generally, the sulfonated styrene/maleic anhydride copolymers suitable for use in the compositions of the present invention will have a molecular weight (weight average) from 5000 to 100,000. The ratio of styrene sulfonic acid to maleic anhydride in the copolymers suitable for use in the compositions of the present invention will range from 2:1–4:1, and will preferably be about 3:1. The compositions of the present invention comprise a sulfonated styrene/maleic anhydride copolymer in an amount effective to enhance the selected drug's solubility or comfort. In general, the amount of sulfonated styrene/maleic anhydride copolymer will range from 0.1 to 10%, preferably 1 to 5%, and most preferably 2 to 4%.

In addition to a drug and a sulfonated styrene/maleic anhydride copolymer, the compositions of the present invention include a cationic preservative such as quatemary ammonium compounds including, but not limited to benzalkonium chloride, benzododecinium bromide, and polyquatemium-1. The amount of preservative to be included in the compositions of the present invention will generally range from 0.001 to 0.03%, preferably 0.001 to 0.015%.

The compositions of the present invention may also include one or more ingredients conventionally found in aqueous ophthalmic, otic or nasal formulations, such as surfactants (e.g., polysorbates, polyethoxylated castor oil derivatives and tyloxapol), viscosity-imparting agents (e.g., carbomer 974P, polyvinyl alcohol or hydroxypropyl methylcellulose), chelating agents (e.g., edetate disodium) and tonicity agents (e.g., sodium chloride, glycerin or mannitol). The compositions will also normally include buffering agents, such as borates, acetates, and phosphates, and pH-adjusting agents, such as NaOH, HCI, and tromethamine, to set and maintain the pH at physiologically acceptable pH (ideally between 6.0 and 7.5). The composi-